

REMARKS

Amendments to the specification:

Applicants have herein amended the priority claim to contain the priority recitation presented in the preliminary amendment submitted along with the filing of the present application. No new matter is added by this amendment.

Claim Rejections under 35 U.S.C. § 101

Utility:

The Office maintains rejection of claims 27-34 under 35 U.S.C. § 101 alleging that the claimed invention is not supported by a substantial utility. In particular, although the Office recognizes there are some references that demonstrate a correlation between gene amplification and protein overexpression, the Office maintains that another reference, by Pennica *et al.*, does not demonstrate such a correlation. Thus, the Office action concludes that because of the unpredictability in the art, "each gene expression analysis must be performed in order to determine definitively whether protein correlates with mRNA levels." (Page 4 of the Office action mailed July 21, 2005). Additionally, the Office action alleges that "it appears that the half-life of the protein is important for use as a diagnostic marker and if a [protein has a] short half-life this would add to the unpredictability of using SEQ ID NO:69 as a diagnostic marker."

Applicants respectfully disagree that claims 27-34 are not supported by any specific, substantial, and credible utility. Applicants respectfully maintain that the Office applies an improper legal standard in rejecting the asserted utility of the claimed polypeptides. For example, the Office argues a definitive determination of whether protein levels correlate with mRNA levels must be made for each gene expression analysis. However, a definitive determination is not required to satisfy the utility requirement. Instead, all that is required is that the Applicant shows that the totality of the evidence demonstrates that the Office has NOT established that it is more likely than not that one of ordinary skill in the art would doubt that mRNA expression levels correlate with protein expression levels. See *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443,

1444 (Fed. Cir. 1992). Significantly, the Applicant only has this burden if the Office has succeeded in making a *prima facie* case of lack of utility. See e.g. MPEP § 2107. To make a *prima facie* case of lack of utility, the Office must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the Applicants' statement of utility. Applicants respectfully maintain that the Office has not made such a *prima facie* case.

Applicants' statement of utility for the PRO357 polypeptide may be found at least at page 137 of the specification. In particular, at page 137 Applicants assert that the claimed PRO357 polypeptide is useful as a diagnostic marker because PRO357 is encoded by a nucleic acid that is amplified in lung and colon tumors. Indeed, the specification discloses that the gene encoding the PRO357 polypeptide showed significant amplification, ranging from 2-fold to more than 8-fold in 40 different lung and colon primary tumors and tumor cell lines, a majority of those tumors and cell lines tested. In addition, Applicants submitted with their Response mailed November 3, 2003, the Declaration of Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer.

To make a *prima facie* case overcoming this assertion of utility by Applicants, the Office must establish that more likely than not, one of ordinary skill in the art would doubt the truth of Applicants' assertion that the claimed polypeptides have utility as diagnostic markers. Applicants respectfully maintain that the sole reference cited by the Examiner, Pennica *et al.*, does not suffice to make a *prima facie* case that more likely than not no generalized correlation exists between gene amplification and increased polypeptide levels. The Examiner maintains that Pennica *et al.* teach that it is unpredictable whether gene amplification and protein overexpression correlate because Pennica *et al.* provide at least one example where no correlation is seen. Applicants previously focused on two other examples in the Pennica reference that show some correlation and stated that the third example relied on by the Examiner should be disregarded because the authors stated the conclusion that no correlation was seen might be based on inaccurate results. However, even if all examples in the Pennica reference are

considered, the teachings of the Pennica *et al.* reference by itself are not sufficient to make it more likely than not that no generalized correlation exists because the teachings of Pennica *et al.* are not directed towards genes in general but rather to a single gene or genes within a single family. Thus, the teachings of Pennica *et al.* cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels.

Yet, even if the Office maintains that the teachings of Pennica *et al.* are sufficient to support a *prima facie* case of lack of utility, in maintaining this rejection, the Office must consider the totality of the record of evidence. Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Bermont *et al.*, Varis *et al.*, and Hu *et al.* (made of record in Applicants' Responses mailed 8 November 2004 and 27 April 2005) collectively teach that in general, gene amplification increases mRNA expression. Second, Applicants also have submitted substantial opinion evidence from qualified experts including the declarations of Audrey Goddard, Ph.D and Avi Ashkenazi, Ph.D. (submitted with Applicants' Response mailed November 3, 2003), and herein submit a third declaration. In particular, please find enclosed with this response a declaration of Paul Polaskis, Ph.D., principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. Dr. Polaskis declares that in general, there is a correlation between mRNA levels and polypeptide levels. More specifically, Dr. Polaskis explains:

4. In the course of the research conducted by Genentech's Tumor Antigen Project . . . using microarray analysis, we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed.

5. From the mRNA and protein expression analyses described in paragraph 4 above, we have observed that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells.
6. Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

Significantly, Dr. Polaskis declares that "in approximately 80%" of the cases observed in connection with the Tumor Antigen Project, increases in the mRNA levels correlated with changes in the levels of protein expression. Thus, this is direct evidence that the art is not unpredictable. Moreover, according to MPEP § 2107, the Examiner "must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." (emphasis added).

Applicants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars of sales in their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.*, that it is more likely than not informative of the protein level).

Thus, when the evidence discussed above is considered in totality, although there are some examples in the scientific art, such as those disclosed by Pennica *et al.*, that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Varis *et al.*, Bermont *et al.*, Hu *et al.*, and the Goddard and Polaskis Declarations, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels.

These teachings are not altered by the statement in the Office action, which is based on a statement in Orntoft *et al.*, that the half-life of a protein may be important in determining the utility of a PRO357 polypeptide as a diagnostic marker. The references relied on by Orntoft *et al.* for the proposition that protein half-life may be important only look at whether there is a correlation between gene and protein expression levels in non-cancerous liver cells or non-human yeast cells. See Anderson, L and Seilhamer, J. 1997. "A comparison of selected mRNA and protein abundances in human liver." *Electrophoresis*, 18(3-4):533-7; Ideker *et al.* 2001. "Integrated genomic and proteomic analyses of a systematically perturbed metabolic network." *Science*, 292:929-934. In contrast, the Orntoft reference itself reviews correlation of expression levels in cancerous tumors of human bladders and reports a "striking correspondence" between gene amplification and protein overexpression. Orntoft at 44 (emphasis added).

When considered in totality, as the evidence must be, MPEP § 2107, even in combination, the Pennica *et al.* reference and the statement in Orntoft *et al.* regarding protein half-life, do not outweigh the teachings exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Varis *et al.*, Bermont *et al.*, Hu *et al.*, and the Goddard and Polaskis Declarations. "Only when the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained." MPEP § 2107 (emphasis added). Thus, Applicants respectfully submit that in view of the substantial evidence discussed above, the maintained rejection of claims 27-34 for alleged lack of utility is improper.

Moreover, Applicants submit that even if there is no correlation between gene amplification and increased mRNA/protein expression, (which Applicants expressly do not concede), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Applicants submit that as evidenced by the Ashkenazi Declaration (submitted with Applicants' Response mailed 3 November 2003), and the teachings of Hanna and Mornin (Pathology Associates Medical Laboratories, August (1999), attached herewith), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor as demonstrated by the real-world example of the breast cancer marker HER-2/neu.

Applicants note that the Office rejects Applicants' assertion of a utility based on use of the PRO357 polypeptide in competitive binding assays with the acid labile subunit of insulin-like growth factor (ALS). Applicants further note that the Office action cites several articles in support of the proposition that "[g]enerally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases." (Page 6 of the Office action mailed July 15, 2005). Although Applicants respectfully disagree and maintain that PRO357 polypeptides may be used in competitive binding assays with the acid labile subunit of ALS, Applicants respectfully submit that it is not necessary to establish this alternative utility of PRO357 polypeptides because the law only requires that an applicant provide "one credible assertion of a specific and substantial utility for each claimed invention to satisfy the utility requirement." MPEP § 2107 (emphasis added). Applicants respectfully maintain that for the reasons discussed above, the claimed PRO357 polypeptides at least are supported by a diagnostic utility. Therefore, Applicants respectfully request that the rejection of claims 27-34 for alleged lack of utility be withdrawn.

35 U.S.C. § 112 ¶ 1, Enablement-Utility

The Office maintains rejection of claims 27-34 under 35 U.S.C. § 112 ¶1, alleging that because the claimed invention is not supported by either a specific asserted utility or a

well established utility, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, addressing the rejection under 35 U.S.C. § 101 for lack of utility, Applicants respectfully submit that the claimed polypeptide is supported by a specific, substantial, and credible utility. Thus, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 27-34 under 35 U.S.C. § 112 ¶1 for their alleged inadequate disclosure on how to use the claimed invention.

Enablement:

The Office also maintains rejection of Claims 27-34 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In particular, the Office action alleges that the claims are not enabled due to the unpredictability in art expression of mRNA and correlation with polypeptide expression. Specifically, the Office action alleges that "it appears from the prior art that each gene expression analysis must be performed in order to determine definitively whether protein correlates with mRNA levels." Thus, the Office action concludes that "[i]n view of the lack of guidance, lack of examples, and lack of predictability in the art . . . one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention."

Applicants respectfully disagree. In *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), the Federal Circuit stated:

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art (citations omitted). The test is not merely quantitative, since a *considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable*

amount of guidance with respect to the direction in which the experimentation should proceed

(emphasis added). In order to determine whether any required experimentation is undue, the Federal Circuit set forth the following factors for consideration: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the level of predictability in the art; (5) the existence of working examples; (6) the breadth of the claims; (7) the amount of direction or guidance by the inventor; and (8) the quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Consideration of the above factors demonstrates that any experimentation necessary to practice the claimed invention would not be undue.

(1) Nature of the Invention

Claimed herein is an isolated polypeptide comprising the amino acid sequence of the polypeptide shown in Figure 26 (SED ID NO:69); the same amino acid sequence lacking its associated signal peptide; the amino acid sequence of the extracellular domain of the polypeptide shown in Figure 26 (SEQ ID NO:69); the same amino acid sequence lacking its associated signal peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209527. Thus, the claims are directed to a well-defined class of polypeptides having the above defined amino acid sequences.

(2) State of the Prior Art

The state of the prior art is advanced. Analysis of the prior art as of the effective filing date of the present application shows that skilled artisans are able to routinely produce, isolate, and analyze nucleic and amino acid sequences. In addition, skilled artisans routinely perform various functional assays using such nucleic and amino acid sequences.

(3) Relative Skill of those in the Art

The relative skill of those in the art is advanced.

(4) Level of Predictability in the Art

The Office action asserts that the art is unpredictable regarding whether gene amplification correlates with protein overexpression. Applicants respectfully disagree. As discussed above with regard to the rejection under 35 U.S.C. § 101, it is generally accepted in the art that gene amplification correlates to increased mRNA levels and that mRNA levels correlate with polypeptide levels. See pages 6-11 above and the Declaration of Dr. Polaskis (attached hereto).

(5) Existence of Working Examples

According to MPEP § 2164.01(b), “as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).” Applicants disclose at least one method for making and using the claimed invention.

It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. The gene amplification assay, well-described in Example 28, pages 119-137 of the present application, sets forth one method for making or isolating a PRO357 nucleic acid encoding the PRO357 polypeptide. Example 28 discloses that the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9. As a negative control, DNA was isolated from the cells of ten normal, healthy individuals. Gene amplification was monitored using real-time quantitative TaqMan™ PCR. Table 10 shows the resulting gene amplification data. Further, Example 28 explains that the results are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to a 4-fold amplification, 3 units correspond to an 8-fold amplification and so on.

A ΔCt value of at least 1.0 was observed for PRO357 in 40 of the tumors and tumor cell lines listed in Table 9. Indeed, PRO357 showed approximately 1.05 to 3.51 ΔCt units, which corresponds to $2^{1.05}$ to $2^{3.51}$ -fold amplification in primary lung and colon tumors and tumor cell lines. Accordingly, the present specification clearly discloses evidence that the gene encoding the PRO357 polypeptide is amplified in a number of lung and colon tumors.

Based on the data provided in Example 28 of the present specification, as discussed above at pages 6-11, one of ordinary skill in the art would be enabled to use the claimed polypeptides, at least as diagnostic markers, because it is generally accepted in the art that gene amplification correlates with protein overexpression.

(6) Breadth of the Claims

Claims 27-34 are not overly broad. Instead they are directed towards a well-defined class of polypeptides as discussed above with regard to factor (1).

(7) Amount of Direction or Guidance by the Inventor

One important characteristic of the claimed polypeptides is that they are encoded by nucleic acids which are amplified in lung or colon tumors. Page 69 of the specification discloses that gene amplification "may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA, dot blotting, or *in situ* hybridization using an appropriately labeled probe, based on the sequences provided herein." Example 28, found at pages 119-137 of the specification, shows that PRO357-encoding genes are amplified in the genome of lung and colon tumors and cell lines.

In addition to describing various characteristics of PRO357, the specification describes various methods that might be used to isolate a PRO357 nucleic acid or polypeptide. For example, page 64 describes producing a PRO357 polypeptide by culturing cells transformed or transfected with a vector containing a PRO357 nucleic acid, such as the nucleic acid of SEQ ID NO:68. Additionally, the specification teaches that direct peptide

synthesis using solid-phase techniques, or *in vitro* protein synthesis using manual techniques or automation may be used to obtain a PRO357 polypeptide of the present invention.

(8) Quantity of Experimentation Needed to Make or Use the Invention

Although some experimentation might be required to practice the claimed invention, the specification provides sufficient guidance to enable one of ordinary skill in the art to make and use the claimed PRO357 polypeptide. Applicants again note that even a “considerable amount of experimentation is permissible, if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *In re Wands*, 858 F.2d 731,737 (Fed. Cir.1988).

Accordingly, Applicants respectfully request that the Examiner withdraw his rejection of Claims 27-34 under 35 U.S.C. § 112, first paragraph for lack of enablement.

Priority

Applicants have herein amended the priority claim to recite the priority claim recited in the preliminary amendment submitted with the filing of the present application. This is the priority claim that was pending in the present case prior to amendment of the priority recitation in Applicants’ Response submitted April 27, 2005.

Claim Rejections under 35 U.S.C. § 102(b)

The Office action rejects claims 27-34 under 35 U.S.C. § 102(b) as being anticipated by Botstein *et al.* (WO 99/35170, published 7/15/99). Anticipation under 35 U.S.C. § 102(b) requires that “the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, *more than one year prior to the date of application for patent in the United States.*”

An application for a patent based on the present invention was filed at least as early as December 22, 1998, which is prior to the publication date of the cited reference. In particular, the PRO357 polypeptide and amino acid sequences are disclosed in U.S. Provisional Application Serial No. 60/113,296 ("the '296 application"), filed 12/22/1998. More specifically, the nucleic acid sequence encoding PRO357 is identified as DNA44804 and is shown in Figure 15 (SEQ ID NO:15) of the '296 application. This sequence corresponds to Figure 25 (SEQ ID NO:68) in the present application. The amino acid sequence encoding PRO357 is shown in Figure 16 (SEQ ID NO:16) of the '296 application, which corresponds to Figure 26 (SEQ ID NO:69) in the present application.

As an application for a patent based on the present invention was filed at least as early as December 22, 1998, Applicants respectfully submit that rejection of claims 27-34 under 35 U.S.C. § 102(b) based on the Botstein reference (WO 99/3517, published 7/15/99) is improper and respectfully request that this ground of rejection be withdrawn.

Conclusion

Applicants believe that currently pending Claims 27-34 are patentable. Applicants respectfully request the Examiner grant allowance of this application. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite the prosecution this application.

Respectfully submitted,

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